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Original Article

Psychiatry/Mental Health Section

Comparison of Functioning, Quality of Life, and Cognition between Lithium and Sodium Valproate Combination Therapy and Sodium Valproate Monotherapy in Euthymic Bipolar Patients: A Cross-sectional Study

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ABSTRACT

Introduction: The combination of lithium and valproate is the most recommended treatment for relapse prevention in Bipolar Affective Disorder (BPAD) after the failure of monotherapy. If it is proven that functioning, quality of life and cognitive functioning in bipolar patients on a sodium valproate and lithium combination are better than those on valproate monotherapy, this could further encourage the use of combination therapy.

Aim: To compare the functioning, quality of life and cognitive functioning of euthymic bipolar patients on lithium and sodium valproate combination therapy with those on sodium valproate monotherapy.

Materials and Methods: The present hospital-based cross-sectional study was conducted in the Outpatient Department, Institute of Mental Health, Madras Medical College, Chennai, Tamil Nadu, India, from March 2017 to July 2017. A total of 80 patients were included in the study. Forty euthymic bipolar disorder patients on a lithium and sodium valproate combination for at least a year were chosen as group 1. Forty euthymic bipolar patients on sodium valproate monotherapy for at least a year were chosen as group 2. Socio-demographic details and clinical characteristics of both groups were collected. The Global Assessment of Functioning (GAF) scale and the World Health Organisation Quality of Life Brief (WHOQoL-BREF) version scale were applied to both groups. Cognitive assessment using the Frontal Assessment Battery (FAB), Trail Making Test-A (TMT-A) and Trail Making Test-B (TMT-B) was conducted. Statistical analysis was performed using International Business Machines (IBM) Statistical Package for Social Sciences (SPSS) software version 20.0. An independent t-test was used to compare quality of life and cognitive variables, as well as, the number of episodes post-treatment between the two groups. A Chi-square test was used to compare functioning between the two groups.

Results: The mean±Standard Deviation (SD) age of onset in group 1 was 26.73±5.77 years and in group 2 was 27.03±6.49 years. There were 22 (55%) males and 18 (45) females in group 1 and, 20 (50) males and 20 (50) females in group 2. There were no statistical differences in socio-demographic characteristics between both groups (p-value>0.05). Functioning and quality of life were significantly better in the combination therapy group (p-value ≤0.01). Cognitive variables like FAB score, and time taken to complete TMT-A and TMT-B in seconds showed no significant differences (p-value>0.05). By independent t-test, the reduction in episodes of bipolar illness after treatment was found to be greater in group 1 (p-value=0.006).

Conclusion: The functioning, quality of life and effectiveness of treatment for those euthymic bipolar patients on lithium and sodium valproate combination therapy were found to be better than those on valproate monotherapy alone. There was no significant change in cognitive functioning between the two groups.

Keywords: Frontal assessment battery, Global assessment of functioning, Major depressive disorder, Mania, Trail making test, Young mania rating scale

INTRODUCTION

Bipolar Affective Disorder (BPAD) is a complex episodic illness characterised by high suicidality and co-morbidity, which requires an equally complex pharmacological therapy [1]. Evidence has been accumulating since the 1990s that recovery from bipolar illness is not complete, particularly regarding psychosocial difficulties, as well as, cognitive deficits [2]. BPAD often shows recovery over time with longer durations of treatment, but there is also a marked tendency for recurrence. Additionally, sudden treatment discontinuation can cause serious effects [3]; improper treatment can lead to a greater number of episodes and increased hospitalisations [4]. All these factors impose significant psychological, as well as, socio-economic burdens on patients and caregivers [2]. Consequently, the impact of the illness affects longevity, relationships, careers and self-esteem [4]. Quality of life in BPAD can be affected even by the depressive symptoms associated with bipolar disorder [5].

Lithium has been the gold standard maintenance treatment for BPAD for more than forty years, as it reduces relapse and suicide risk. However, it has been found to be ineffective for some patients due to its narrow therapeutic index and adverse effects, which can lead to suboptimal adherence [6-9]. This has prompted the search for alternative treatments, one of which is sodium valproate, known for its antimanic and relapse prevention properties [10,11].

Since many patients do not seem to respond to monotherapy, drug combinations are often recommended, despite the limited evidence supporting this approach [12]. The combination of lithium and valproate is the most recommended treatment after the failure of monotherapy used as first-line treatment [6,13]. If this combination demonstrates synergistic pharmacological effects, it may prove to be more effective than monotherapy and could even be used as a first-line therapy [14-16]. However, comparisons between this combination and monotherapy have rarely been conducted in the

past [2]. The Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) trial was an important large study that established that the combination of valproate semisodium and lithium is more effective than valproate monotherapy [17].

Bipolar patients exhibit neurocognitive deficits compared to healthy controls, even during the euthymic period once symptoms have resolved [18-20]. Despite years of scientific research, the nature, extent and pattern of these cognitive deficits remain the focus of debate, as well as, research [21], as some studies suggest that cognition is not affected in bipolar disorder [22]. While valproate has been observed to impact attention, cognitive flexibility and verbal memory in BPAD patients in several studies [23,24], lithium has been found to affect psychomotor functioning, speed, response inhibition ability and memory [25]. Conversely, the literature also addresses the neuroprotective effects of lithium, along with valproate [26,27]. Both lithium and valproic acid have demonstrated neuroprotective properties in vivo and in vitro. Synergistic neuroprotective effects of this combination treatment have been observed against glutamate-induced excitotoxicity in cultured neurons of the brain, by potentiating the inhibition of Glycogen Synthase Kinase-3 (GSK-3) activity [28].

Given the inconsistency in the literature regarding the effects of lithium and valproate on cognitive functions in BPAD patients, the present study was aimed to compare neurocognition between the combination therapy and valproate monotherapy to determine if the synergism provides neuroprotection, as stated in an article that dealt with in vitro settings [29,30].

Thus, the aim of the present study was to compare functioning, quality of life, and certain neurocognitive domains in euthymic bipolar patients receiving lithium and sodium valproate combination therapy with those on sodium valproate monotherapy. According to the null hypothesis, there is no difference in functioning, quality of life, and cognition in euthymic patients between the combination therapy and monotherapy.

MATERIALS AND METHODS

The present hospital-based cross-sectional study was conducted in the Outpatient Department, Institute of Mental Health, Madras Medical College, Chennai, Tamil Nadu, India, from March 2017 to July 2017. Ethical committee approval was obtained in March 2016 (NCT No. 23012017). Apart from receiving medications used for the present study, both groups were also receiving other medications, including anticholinergics, antipsychotics and benzodiazepines. Euthymia was confirmed by two senior psychiatrists in addition to the rater, with the Young Mania Rating Scale (YMRS) score ≤10 [23,31] and the Hamilton Depression Rating Scale (HAM-DRS) score ≤7 [32,23].

Inclusion criteria: Two groups were selected for the study. Group 1 consisted of forty patients with BPAD, diagnosed according to ICD-10, who had been on a combination of lithium (600-1200 mg) and sodium valproate (400-1200 mg) as mood stabilisers for at least one year. Group 2 comprised forty patients diagnosed with bipolar disorder according to ICD-10, who had been on sodium valproate monotherapy (600-1200 mg) -as a mood stabiliser for at least one year. Participants in both groups were aged between 20 years and 55 years, who gave written consent to participate in the study, and were euthymic for at least six months were included in the study.

Exclusion criteria: In both groups, individuals with other mental disorders, uncontrolled medical conditions, neurological disorders, learning difficulties and a past history of electroconvulsive therapy were excluded from the study.

Sample size calculation: In similar studies, the number of participants was 30 or fewer in each group [2,23,33,34]. The sample size was calculated using G*Power software with an effect size of 0.8 (Cohen's D was 0.8 in the LIVACAL study) [33], an alpha error probability of 0.03, and a power of 0.95, resulting in 40 participants in each group, for a total sample size of 80.

Study Procedure

The study subjects were informed about the nature of the study, and consent was obtained from them. Socio-demographic details were collected using a semi-structured proforma, along with clinical characteristics of both groups. A complete physical examination, including a detailed neurological evaluation was conducted. Subsequently, all subjects were assessed for the following:

Functioning by the Global Assessment Functioning (GAF) scale [35]: This is a numerical scale used subjectively by clinicians to rate the occupational, social and psychological functioning of an individual. Scores range from 100 (extremely high functioning) to 1 (severely impaired) across the following 10 codes: 91-100, 81-90 and so on down to 1-10. A code is assigned as 0 when the information available is inadequate. The advantage of this scale, which belongs to the Diagnostic and Statistical Manual-IV (DSM-IV), is its brevity [35].

Quality of Life by the World Health Organisation Quality of Life-Brief (WHOQoL-BREF) version scale [36]: This shorter version of WHOQoL-100 is a self-administered questionnaire comprising 26 questions about the individual's perceptions of their health and well-being. It covers four domains, namely physical health, psychological health, social relationships and environmental domains. There are also two separate questions that ask about the individual's overall perception of their health and their quality of life. Each item is scored on a Likert scale from 1 to 5. Mean scores for each domain are calculated and multiplied by 4 to make the scores comparable to the WHOQoL-100. A conversion table is used to convert raw scores to transformed scores on a scale of 0 to 100. Higher scores in each of the domains indicate higher personal satisfaction in that specific domain [36].

Cognitive assessment using FAB [37], TMT-A [38] and TMT-B [38]: The neuropsychological tool, FAB, was devised by Dubois B et al. [37]. It is brief and helps assess executive functions at the bedside. The FAB has six subtests that widely cover the functions of the frontal lobes. Each subtest has a score from 0 to 3, with a maximum score of 18. A score of 12 or below is considered abnormal, while higher scores indicate better performance. Here, executive functions like conceptualisation, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy are assessed using the similarities task, phonological fluency task, Luria's motor series, conflicting instructions task, go-no-go task and prehension behaviour, respectively [37]. TMT-A and TMT-B are part of the Halstead-Reitan Battery. TMT-A requires subjects to connect 25 consecutively numbered circles. In part B, 25 numbered and lettered circles must be connected by shifting between the two sets, i.e., 1-A, 2-B, 3-C and so on. The time taken to complete these tasks is recorded in seconds. Part A measures psychomotor speed, while part B reflects the ability to shift strategies and assesses executive function, visuospatial working memory and cognitive processing speed [38].

Tests were administered in a quiet room in a fixed, preset order according to standard administration instructions. The time taken was approximately one hour to one hour and thirty minutes. Assessments were carried out in one to two sessions, with each session not extending beyond one hour.

STATISTICAL ANALYSIS

The statistical analysis was conducted using IBM SPSS software version 20. The Chi-square test and Independent t-test were applied to compare the socio-demographic characteristics of the combination group and the monotherapy group. The independent t-test was used to compare the quality of life and the number of episodes before and after treatment, as well as, the cognitive

variables between the two groups. The Chi-square test was employed to compare the functioning of the two groups.

RESULTS

Group 1 patients, who were on combination therapy, had a mean age of onset of 26.73±5.77 years, with an average duration of illness of 9.95±7.51 years, and sodium valproate (400-1200 mg) was used for the entire duration of illness. Lithium (600-1200 mg) was added to all patients after an average of 5.425±4.936 years. Group 2 patients, who were on valproate monotherapy, had a mean age of onset of 27.03±6.49 years, with an average duration of illness and valproate intake of 9.38±7.51 years. No significant difference was observed between the groups for mean age of onset, duration of treatment and total number of episodes (manic and depressive) before treatment (p-value>0.05). However, patients in group 1 had a significantly lesser number of manic and depressive episodes after treatment (p-value<0.05) [Table/Fig-1].

Clinical characteristics (mean±SD)[∞]	Group 1	Group 2	p-value
Age of onset (years)	26.73±5.77	27.03±6.49	0.83
Duration of illness in years	9.95±7.51	9.38±7.51	0.73
Total number of episodes (manic and depressive) before treatment	4.9±3.85	5.0±4.01	0.91
Dosage of drugs (mg)	SVP[$]: 930±273.81 Lithium: 937.5	945±248.02	0.798
Duration of treatment (years)	5.425±4.936	9.125±7.328	0.01*
Number of manic episodes after treatment	0.88±1.07	2.85±2.72	<0.0001*
Number of depressive episodes after treatment	0.25±0.59	1.275±1.92	0.0018*

[Table/Fig-1]: Clinical characteristics of both groups.
[∞]SD: Standard deviation; [$]SVP: Sodium valproate; *The p-value <0.05 was considered statistically significant

In the present study, there were 22 (55%) males and 18 (45) females in group 1 and, 20 (50%) males and 20 (50%) females in group 2. The Chi-square test was applied for the socio-demographic comparison pertaining to gender, occupation, marital status, education and occupation between the two groups. An independent t-test was used to compare age between both groups. The p-values for all categories were >0.05, suggesting that there was no statistical significance between the two groups [Table/Fig-2,3].

Variables		Groups		
		Group 1 n (%)	Group 2 n (%)	p-value
Sex	Male	22 (55)	20 (50)	0.317
	Female	18 (45)	20 (50)	
Marital status	Married	22 (55)	23 (57.5)	0.114
	Single	12 (30)	12 (30)	
	Separated	4 (10)	2 (5)	
	Widow/widower	2 (5)	3 (7.5)	
Education group	Primary and secondary	37 (92.5)	38 (95)	0.251
	Degree/Diploma/PG	3 (7.5)	2 (5)	
Occupation group	Unemployed/ Homemaker	14 (35)	17 (42.5)	0.186
	Unskilled	14 (35)	11 (27.5)	
	Semi-skilled/Skilled	12 (30)	12 (30)	

[Table/Fig-2]: Comparison of socio-demographic data of both groups.

Using the Chi-square test, a significant difference in functioning between the two groups was found (χ^2 value-22.224, p-value=0.001). A total of 29 out of the 40 patients in group 1 had functioning in the range of 71-100, while in group 2, 30 out of the 40 patients were in the range of 41-70. Eight patients from the first group had functioning in the range of 91-100, while only one from the second group belonged to the same range [Table/Fig-4].

Groups	n	Mean	Standard deviation	Standard error mean	t-value	p-value
Group 1	40	36.675	9.804	1.550	0.124	0.902
Group 2	40	36.400	10.030	1.586		

[Table/Fig-3]: Comparison of the two groups' ages.

GAF scores	Group 1, n (%)	Group 2, n (%)	Total, n (%)
41-50	2 (5)	7 (17.5)	9 (11.2)
51-60	3 (7.5)	16 (40)	19 (23.8)
61-70	6 (15)	7 (17.5)	13 (16.2)
71-80	16 (40)	7 (17.5)	23 (28.8)
81-90	5 (12.50)	2 (5)	7 (8.8)
91-100	8 (20)	1 (2.5)	9 (11.2)
Total	40 (100)	40 (100)	80 (100)

[Table/Fig-4]: Comparison of GAF scores between the two groups.
Chi-square value=22.224; p-value=0.001

Each domain of the WHOQoL-BREF scale was compared between the two groups using an Independent t-test [Table/Fig-5]. Patients in group 1 had significantly better scores in the physical, psychological, environmental and social domains of WHOQoL-BREF compared to group 2 (p-value<0.001). Overall quality of life and health satisfaction scores were compared between the two groups using the independent t-test and were found to be better in group 1 (p-value<0.05) [Table/Fig-6].

WHOQoL-BREF domains	Groups	n	Mean	Standard deviation	Std. error mean	t-value	p-value
Physiological	Group 1	40	76.4000	14.31657	2.26365	7.160	<0.001*
	Group 2	40	50.8500	17.44816	2.75880		
Psychological	Group 1	40	73.6750	18.71704	2.95942	5.374	<0.001*
	Group 2	40	51.7750	17.72075	2.80190		
Social	Group 1	40	76.4750	16.57924	2.62141	4.827	<0.001*
	Group 2	40	57.4000	18.70253	2.95713		
Environmental	Group 1	40	75.1500	17.53027	2.77178	4.195	<0.001*
	Group 2	40	58.4000	18.17691	2.87402		

[Table/Fig-5]: Comparison of WHOQoL-BREF domains between the two groups.

Parameters	Groups	n	Mean	Standard deviation	t-value	p-value
Overall QoL score	Group 1	40	4.45	0.51	2.22	0.0296*
	Group 2	40	4.08	0.64		
Health satisfaction	Group 1	40	4.53	0.46	2.31202	0.0234*
	Group 2	40	4.18	0.46		

[Table/Fig-6]: Comparison of overall quality of life and health satisfaction between the two groups.

An independent t-test was used to compare the cognitive variables like FAB total score and individual items, as well as, the time taken to perform TMT-A and TMT-B in seconds between the two groups [Table/Fig-7]. There was no significant difference between the FAB total score and individual items, as well as the time taken to perform TMT-A and TMT-B between the two groups (p-value>0.05).

In [Table/Fig-8], an independent t-test was used to compare the reduction of episodes after treatment in both groups. The difference was statistically significant with combination therapy (p-value<0.001).

Using the Pearson's Chi-square test, it was found that 17.5% of group 2 had three or more depressive episodes post-treatment, while no one in group 1 had three or more depressive episodes.

Parameters	Groups	N	Mean	Std. deviation	Std. error mean	t-value	p-value
FAB total score	Group 1	40	14.6250	3.27921	0.51849	0.129	0.898
	Group 2	40	14.5250	3.63732	0.57511		
FAB-similarities score	Group 1	40	2.5500	0.59700	0.09439	1.359	0.178
	Group 2	40	2.7250	0.55412	0.08761		
FAB-lexical fluency score	Group 1	40	2.3000	0.68687	0.10860	0.641	0.524
	Group 2	40	2.4000	0.70892	0.11209		
FAB-Motor Luria score	Group 1	40	1.9750	0.89120	0.14091	0.127	0.9
	Group 2	40	1.9500	0.87560	0.13844		
FAB-conflicting instructions score	Group 1	40	2.5500	0.71432	0.11294	1.027	0.307
	Group 2	40	2.3750	0.80662	0.12754		
FAB-go-no-go test score	Group 1	40	2.6000	0.59052	0.09337	1.371	0.174
	Group 2	40	2.4000	0.70892	0.11209		
FAB-prehension behaviour score	Group 1	40	2.7000	0.46410	0.07338	0.225	0.822
	Group 2	40	2.6750	0.52563	0.08311		
TMT-A* (time in secs)	Group 1	40	55.83	23.431	3.705	1.756	0.083
	Group 2	40	47.35	19.561	3.093		
TMT-B** (time in secs)	Group 1	40	273.18	26.746	4.229	-0.293	0.771
	Group 2	40	275.03	29.714	4.698		

[Table/Fig-7]: Comparison of cognitive variables between the two groups.
TMT-A: Trail making test-A; TMT-B: Trail making test-B

Parameters	Groups	n	Mean	Std. deviation	Std. error mean	p-value
Number of episodes before treatment	Group 1	40	4.900	3.8484	0.60849	0.910
	Group 2	40	5.000	4.0064	0.63347	
Number of episodes after treatment	Group 1	40	1.125	1.5053	0.23801	<0.001*
	Group 2	40	4.050	4.0252	0.63645	

[Table/Fig-8]: Comparison of number of episodes (manic and depressive) between groups 1 and 2 before and after treatment.

Additionally, 27.5% of group 2 and 17.5% of group 1 had one or two depressive episodes, while 82.5% of group 1 and 55% of group 2 had no depressive episodes. Thus, the number of depressive episodes was found to be reduced in the group receiving both lithium and sodium valproate when compared to the monotherapy group (p-value=0.006) [Table/Fig-9].

Number of depressive episodes after treatment	Groups		Total n (%)
	Group 1 n (%)	Group 2 n (%)	
Zero	33 (82.5)	22 (55)	55 (68.8)
One to two	7 (17.5)	11 (27.5)	18 (22.5)
More than or equal to three	0	7 (17.5)	7 (8.8)

[Table/Fig-9]: Comparison of frequency of post-treatment depressive episodes between the two groups.
Pearson's Chi-square=10.089; p-value=0.006

DISCUSSION

The findings of the present study indicated that functioning and quality of life were better in the group receiving combination treatment compared to the group receiving valproate alone, thus rejecting the null hypothesis. No differences in cognitive functioning between the two groups were noted.

The GAF scale indicated superior functioning across a wide range of activities among patients treated with a combination of sodium valproate and lithium. These findings suggest that patients in the first group were socially effective, generally satisfied with life, with no more than slight impairment in occupational or social functioning, and exhibited expectable reactions to psychosocial stressors. However, this finding contrasts with the BALANCE study, which reported no statistically significant difference in GAF scores between the lithium-valproate combination and valproate monotherapy [17]. Conversely, a recent case series published this year involving two patients demonstrated that lithium-valproate combination therapy was superior to lithium monotherapy. In this series, Clinical Global Impression Scale scores improved from 4.8 to 2.1, HAM-DRS scores decreased from 25.6 to 9.7, and GAF scores rose from 50.3 to 75.4, with these improvements sustained over a 12-month follow-up period [39].

Another finding in the present study was that quality of life was significantly better in the group receiving sodium valproate and lithium compared to those on sodium valproate alone. This observation is supported by research from Chand PK et al., which indicated that the use of lithium in euthymic bipolar patients led to a better quality of life comparable to that of healthy controls, unlike patients with schizophrenia [40]. In contrast, the BALANCE study reported similar quality of life scores across both treatment groups [17]. Side-effects of the treatment, which were not studied here, could have been one of the reasons for the reduced scores in the physical domain of WHOQoL-BREF in the second group, which could pose a significant burden in terms of increased medical costs and absenteeism, thereby affecting the social domain scores, as well [41].

One of the secondary findings in the present study was the notable reduction in the frequency of illness episodes among patients receiving combination therapy compared to those on monotherapy. Numerous studies have documented that the combination of lithium and sodium valproate yields faster reductions in mania rating scores [2,42]. Furthermore, Geddes JR et al., found in the BALANCE trial that both combination therapy (lithium plus valproate) and lithium monotherapy were more effective at preventing relapse than valproate monotherapy, which aligns with our results [17]. Fengli S et al., also reported significantly lower relapse rates in patients receiving combination therapy compared to those on either lithium or valproate monotherapy [43]. Similarly, Liu Y et al., demonstrated that the lithium-valproate combination was more effective than monotherapy in preventing relapse [13], reinforcing the findings of this study.

Literature states that bipolar patients with a higher frequency of episodes tend to have a poorer quality of life in the euthymic period [44]. The significant reduction in the frequency of bipolar episodes associated with combination therapy may explain the enhanced quality of life and functioning observed in the present study. Moreover, the authors found that combination therapy was more effective in reducing depressive episodes post-treatment, which likely contributed to the improved functioning and quality of life in this group [45]. Khafif TC et al., also concluded in their recent study that longer periods of euthymia were associated with better outcomes in quality of life [46].

Activities that involve personal initiative, like leisure pursuits, may continue to feel abnormal well into the period between episodes [47]. Additionally, impairment in leisure activities and workplace difficulties was especially marked in cases of dysthymia or chronic depression [48]. Uneasiness in the work environment stemming from past disagreements with colleagues during the illness, or difficulty maintaining conflict-free relationships with significant others from the illness phase to the recovery phase, may have contributed to decreased functioning and lower social quality of life in the second group, as these patients had a greater number of depressive episodes after treatment was initiated [48].

Bipolar illness with a higher number of episodes negatively affects cognition [49]. Interestingly, this study showed no significant changes in cognitive variables between the two groups. Many individual studies on lithium have been conducted [20,25]. Neuroimaging in humans also supports that lithium exerts a neuroprotective action [26]. For example, lithium, when used for four weeks as treatment in bipolar patients, was shown to increase N-Acetyl Aspartate (NAA) in a study that involved quantitative proton magnetic resonance

spectroscopy, concluding that chronic lithium increases neuronal viability in the human brain [26]. Fukumoto T et al., concluded in their study that lithium administration for 14 days significantly increased the level of Brain-derived Neurotrophic Factor (BDNF) in the frontal cortices and hippocampus of the rat brain, and in the temporal cortex when used for 28 days, but there was no change in Glial-derived Neurotrophic Factor (GDNF) [27]. An Indian cross-sectional study with 30 participants found that patients on lithium had severe dysfunction in attention and cognitive flexibility over the TMT and executive functions over the Stroop test [25]. A meta-analysis involving four studies concluded that lithium use resulted in only a few minor negative effects on cognition [50]. Another meta-analysis involving 12 studies with 276 subjects on lithium for a mean duration of 3.9 years showed that there were small but significant impairments in immediate verbal learning and memory, whereas delayed verbal memory, visual memory, attention, executive function, processing speed and psychomotor performance were not significantly affected [51]. Thus, the literature regarding the effects of lithium on cognition is mixed [25,50,51].

Muralidharan K et al., concluded that treatment with valproate, rather than lithium, may be associated with working memory deficits early in the course of BPAD, while not affecting other cognitive domains [23]. In a study conducted by Prevey ML et al., patients on valproate showed a subtle compromise in motor speed, coordination, memory, concentration and mental flexibility when compared to controls, although this was similar to findings with carbamazepine [52]. In yet another study, 29 subjects on lithium monotherapy, 28 on lithium plus one or more anticonvulsants and 16 participants on one or more anticonvulsants were compared along with 25 healthy controls. Those on lithium monotherapy had preserved short-term auditory memory, long-term memory and attention; those who took only anticonvulsants showed worse findings in short-term visual memory, working memory and several executive functions; while all groups showed worse performance in processing speed, resistance to interference and emotion recognition when compared to controls [53]. All these studies state that cognition in euthymic bipolar patients on lithium or an anticonvulsant was worse only when compared to healthy controls; otherwise, it was comparable. The synergistic neuroprotective effects of the lithium and valproate combination have been proved in the past [29], but the present study notes no significant improvement when compared to valproate monotherapy.

Limitation(s)

Limitations, like not using control groups, need to be addressed in future studies. The use of other medications, such as anticholinergics, benzodiazepines and antipsychotics, could have interfered with the results. Recruitment from a single treatment centre may limit the degree to which the results of the study can be generalised to other cohorts of patients. Multicentre study would have helped in gathering a larger and more heterogeneous sample for the study, thereby enhancing the generalisability of the findings. The presence or absence of drug side effects and psychosocial interventions may have impacted the quality of life and functioning results and should have been investigated. Additionally, analysing the serum levels of the mood stabilisers could have strengthened the study.

CONCLUSION(S)

The functioning and quality of life of euthymic bipolar patients receiving combination therapy with lithium and sodium valproate were found to be better than those undergoing valproate monotherapy. This improvement can be attributed to the lower relapse rates observed in the present study. Patients on combination therapy experienced significantly fewer manic and depressive episodes. However, there was no notable difference in cognitive functioning between the two groups. The strengths of the present study include matching for age, gender, education, occupation and marital status. The use of standardised diagnostic criteria and rigorous data collection methods enhances the validity and reliability of the findings. As highlighted in the literature, very few studies have compared the combination of lithium and valproate to valproate alone, indicating the need for further research to support the use of combination therapies in clinical practice.

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